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Estimation of Human Toxicity From Animal Inhalation Toxicity Data:
1. Minute Volume-Body Weight Relationships Between Animals And Man

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ESTIMATION OF HUMAN TOXICITY FROM ANIMAL INHALATION TOXICITY DATA: 1. MINUTE VOLUME - BODY WEIGHT RELATIONSHIPS BETWEEN ANIMALS AND MAN.

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ABSTRACT

The relationship between body weight (BW) and respiratory minute volume (V_m) was reviewed by collecting a data base from the literature of minute volume rates that encompassed species from mice at 12 g body weight to horses and a giraffe at ≈500 kg body weight. The data were separated into anesthetized and non-anesthetized groups and juvenile animals were removed from the non-anesthetized group. The final data set of non-anesthetized animals contained 134 studies representing 2304 animals and 18 species. The data show a power-law (allometric) relationship between the minute volume and body weight. The scaling or allometric parameters in this power-law have been estimated using a linear regression of the logarithms of the minute volume against body weight. The resulting allometric equations were;

$$\mathrm{Log}_{10}V_m = -0.286 + 0.802\ \mathrm{Log}_{10}BW \qquad \text{or} \qquad V_m = 0.518\ BW^{0.802}$$

From these equations a corresponding set of minute volumes were obtained for various body weights of humans *eg.* 15.6 L/min for a 70 kg human. The results of the analyses were compared to similar studies in the literature. The relationship is recommended for military uses because it is derived from non-anesthetized, young adult mammals which are expected to mimic the soldier.

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Table I

Comparison of minute volume/body weight data from various literature sources

Species/ Source	C&W [1]	Guyton [2]		Snipes [3]	EPA [4]	This review
	Minute volume/Body weight ratio ($L.min^{-1}.kg^{-1}$)					
Anesthetic	yes	yes	no	no	mix	no
Mouse	0.66	1.15	1.239	1.3	1.152	1.491
Hamster	-	0.500	0.665	-	0.731	0.474
Rat	0.64	0.688	0.638	0.80	0.615	0.881
Guinea pig	0.19	0.323	0.334	0.66	0.475	0.616
Rabbit	0.26	0.387	-	-	0.332	0.413
Cat	0.26	-	-	-	0.335	0.257
Dog	0.25	-	-	0.36	0.258	0.368
Monkey	0.29	-	0.322	0.29	0.257	0.374
Baboon	-	-	-	-	-	0.365
Goat	-	-	-	-	0.235	0.263
Sheep	-	-	-	-	0.298	0.289
Pig	-	-	-	-	0.403	0.138
Donkey	-	-	-	-	0.159	0.163
Pony	-	-	-	-	0.208	0.183
Mule	-	-	-	-	0.248	0.123
Horse	-	-	-	-	0.118	0.131
Cow	-	-	-	-	0.253	0.201
Man (70 kg unless noted)						
- quoted	0.0914	0.127[a]	0.128	0.09	0.286	--
- calculated[b]	0.146	0.142	0.127	0.18	0.164	0.223
Breathing rates for Man (L/min)						
- quoted	6.4	8.7[b]	8.7	20	20	-
- calculated[b]	10.2	10.	8.9	12.4	10.6	15.6

EPA values were derived either from the allometric equations given for combined species or as the average value of data presented for that species [4].

[a] Value for 68.5 kg man.

[b] Values calculated from the matching allometric equations (*vide infra*).

EXECUTIVE SUMMARY

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BACKGROUND

In order to estimate human inhalation toxicity from animal inhalation toxicity data there must be an acceptable formula that describes the relationship between animal and human body sizes and respiration rates[1]. Of necessity, this relationship must be determined empirically from experimental information using a variety of species both smaller and larger than humans. Once the relationship is established, the relationship may be used, in conjunction with toxicity data, to estimate human toxicity, first, from data with small laboratory species and then with increasing confidence as data with larger species are added to the data base.

Because of variation between animals, between techniques and technologies, between anesthetized and non-anesthetized animals and between handling practices in the laboratories, the respiratory data collected over the last century show considerable variability. Fortunately, there are sufficient studies to provide large statistical numbers which tend to reduce the effects of biological, age and sex variability. Furthermore, the experimenters recognized the effects of anesthetics and deliberately collected a great deal of information for non-anesthetized animals. Despite this, some of the most recent reviews of the data have ignored anesthetic use with the result that the collected data and inter-species relationships have greater variability than necessary. In addition, the most recent major review includes a large amount of data from very young animals which again increases the apparent variability in the statistical comparisons between species.

For this review, intended for military uses, data from the literature have been deliberately selected to match the soldier with regard to age and physical development. Anesthetized animal data are reported but not used. Only mammalian data was considered. Data from very young mammals and from mammals adapted to marine life were eliminated. To obtain the closest match of the human to the animal data, the minute volume for the human was taken directly from the calculated allometric rather than arbitrarily assigning a human value as has been done in other studies.

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1 The science of allometry is the study of the biology of scaling *ie.* the effects of body size on physiology, physiognomy and metabolism. For in depth treatment of the topic see [5, 6].

Table II

Recommended values of human minute volumes calculated for a range of body weights

Body weight (kg)	Minute volume (L/min)	Body weight (kg)	Minute volume (L/min)	Body weight (kg)	Minute volume (L/min)
55	12.9	75	16.5	95	20.0
60	13.8	80	17.4	100	20.8
65	14.7	85	18.3	105	21.6
70	15.6	90	29.1	110	22.5

Minute volumes are calculated from the recommended allometric equation.

Table III

Calculated values for the "Standard" laboratory animals

Species	Body weight (kg)	Minute volume (L/min)	Minute volume / Body weight ratio
Mouse	0.025	0.0269	1.0760
Rat	0.250	0.170	0.681
Guinea pig	0.50	0.297	0.594
Rabbit	3.0	1.249	0.416
Dog	10.	3.281	0.328
Ferret	1.1	0.559	0.508
Monkey	4.5	1.729	0.384

RESULTS

The data encompasses 106 papers covering 24 species involving 241 experimental groups and data from 3443 animals. The data were split into anesthetized and non-anesthetized groups. The data for non-anesthetized animals selected represents 18 species, in 134 studies and 2304 land mammals. The animals range in size from mice at 12 g to horses and a giraffe at 480 - 550 kg. Marine adapted mammals were excluded because of the adaptation to underwater life-style involving infrequent breathing and extended breath-holding. Since the ultimate aim was to predict the values in man from those in other animals, the data for man were not included but were calculated from the data. The resulting value for humans compared favourably to published values.

The data provide a linear relationship between the Log_{10} of body weight and the Log_{10} of minute volume[2]. The regression equation may be expressed as either;

$$Log_{10}V_m = -0.286 + 0.802\ Log_{10}BW \qquad \text{or} \qquad V_m = 0.518\ BW^{0.802}$$

where units of minute volume (V_m) and body weight (BW) are L/min and kg, respectively.

From these data, the corresponding value for human respiration for a 70 kg man was calculated to be 15.6 L/min and the corresponding values for a range of breathing rates are given in Table II. Comparing this to literature values for human respiration indicates that the "standard man" would be doing light exercise when breathing at this rate.

The relationship between dose and breathing rate is believed to be linear *ie* as the breathing rate increases, the minute volume increases and the amount of substance inhaled increases in direct proportion. Thus, a man breathing at 30 L/min would inhale 30/15.6 or 1.92 times as much substance as our standard man.

Many literature studies on toxicology do not contain body weight and/or minute volume data on the test subjects. In these cases, data for "standard" animals are used. Values calculated from the allometric relationship above for "standard" laboratory animals are provided in Table III for convenience.

CONCLUSION

The relationship above is recommended for military use because it has been derived from a large data base representing unanesthetized, young adult mammals which should mimic the age and physiologic state of the soldier.

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2 The minute volume is the average volume of air inhaled (or exhaled) in one minute. It varies with body size, excitement, work and tension. It is the product of tidal volume (one breath) and frequency (how many breaths/min).

INTRODUCTION

The assessment of human hazards from chemical exposures, whether deliberate or accidental, requires a knowledge of the differential relationships of metabolism, physiology and respiration between man and other mammalian species[1], particularly those species commonly used for laboratory and agricultural experimentation. The requirement is particularly important when inhalation exposures are to be assessed because the doses received are not directly defined (as in direct injection/feeding routes of chemical introduction) but rather inferred from atmospheric and respiration parameters. With most hazard assessments, there is little information concerning direct human exposures and the toxicity estimates must be made by extrapolating animal data to assess the human condition.

Comparative physiologists and, more recently, toxicologists have provided a wealth of information concerning the relative respiration rates, tidal volumes and other respiratory parameters and several comparative studies have been published [1, 2, 3, 4, 70, 118, 128] relating the body weight, body surface and alveolar surface areas to these parameters in mammals. As technology has improved, the methods of measuring these functions have progressed from procedures requiring anesthesia and surgical intervention [54] to direct measurements on intact animals in enclosed chambers [135] to more modern methods of direct instrumental measurements on restrained but otherwise unmolested animals [106, 118, 129, 133]. In the process, the effects of using no anesthetic [63, 119,], single and combinations of anesthetics [64, 78, 152] have been studied. In retrospect, it is clear that the animal data on respiratory function must be grouped such that the emotional and physiologic state of the animals is as similar as possible and the comparative human values must be matched to similar animal data.

In inhalation toxicology, the dose received by an animal is directly related to the amount of air inhaled [3, 7, 8]. The important inter-related respiratory measurements are the respiration rate, the tidal volume and the minute volume. Several authors have attempted to relate minute volumes to the body weight of animal species [1, 2, 3, 4, 7, 70]. Although the process is generally agreed, the data and resulting mathematical values are quite different (Table I). Although some convergence may be noted in the most recent compilations, these data sets have been promulgated by authors from the same institutes.

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1 The study of the relationships between body size and the physiology and metabolism is the science of allometry. For in depth treatments of the science see References 5 and 6.

Upon investigation, it was apparent that the data in two cases [2, 4] were derived from a mixture of anesthetized and non-anesthetized animals and another [3] could not be readily traced to published data. For this report, a relatively large number of studies providing body weight/respiratory volume data have been collected, reviewed, tabulated and the data compared to previous attempts to related body weight and minute volume. Relationships between body weight and minute volume have been derived for anesthetized and non-anesthetized animals and simplified formulae provided to assist in human hazard assessment from animal toxicity data.

METHODS

The data gleaned from the literature for physiologic condition, body weights, minute volumes and the numbers of animals used were tabulated and mean values for each species and the standard deviation of the data were calculated using FRAMEWORK IV. When the number of data in a group (N value) was less than 4, standard deviations were not reported. The data were divided into anesthetized and non-anesthetized groups. The values for body weight and minute volume were plotted for all the data in each group and for each species in each group and the results evaluated.

A linear regression was calculated for each major group using a log-log relationship between the minute volume and body weight.

The data analysis was conducted using S-PLUS Version 3.4 for UNIX running on a Hewlett-Packard model 715/50 workstation under HP-UX (Hewlett-Packard, 3000 Hanover St., Palo Alto, California). S-PLUS (Mathsoft, Inc., Seattle, Washington) provides an interactive and integrated computing environment consisting of a suite of software facilities for programming, graphics and statistical analysis. All the computations were preformed in double precision (64 bit precision of a 32 bit computer). The computed numbers are carried calculated with 14 decimal places.

RESULTS

EVALUATION OF DATA COLLECTED FROM THE LITERATURE

The full data collection encompasses 106 papers covering 24 species tabulating 241 experimental groups and data from 3443 animals. The animals range in size from mice at 12 g to horses and a giraffe at 480 - 550 kg. The data, summarized in Tables III and IV, were divided into non-anesthetized (Tables III, V) and anesthetized (Tables IV, VI) groups and treated separately. Although data for birds were available and have been used in other summaries [4], they were not included here. Data for man were also excluded because one aim of the study was to obtain theoretical data for man. Several papers shown in the tables are for marine adapted mammals [104, 105, 147]. These data were not included in the final data set because of the adaptation to underwater life-style involving periodic or infrequent breathing and extended breath-holding. Because the ultimate aim was to predict the values in adult man from those in other animals, the data from very young (baby) animals also were excluded. These excluded data are marked with single asterisks in the tables.

When the data for non-anesthetized animals of all species were plotted as Log_{10} of minute volume vs Log_{10} of body weight (Fig. 1) a straight line resulted (power-law curve) with the variability within acceptable limits. In this graph, the data for each species are identified. Analysis of the variability in this data indicated that several studies were indeed statistically separate from the main body of the data. These included the cat studies of Wang [152], the cotton rat data of Guyton [2] and the spiny anteater study by Bentley *et al* [62] which are marked with double asterisks in the data tables. With these data removed, the final data set contained data from 134 studies on 18 species and 2304 animals.

Analysis of the data set

A model for the respiratory system [9] based on a geometrically self-similar (fractal) network of flexible cylindrical tubes shows that the minute ventilation, $\mathbf{V_m}$, and body mass, **BW**, is characterized by an allometric scaling relation of the form

$$\mathbf{V_m} = k\,\mathbf{BW}^{3/4} \qquad (1)$$

where k is a "universal" constant. The power of **BW**, *ie.* 3/4 or 0.75, is referred to as the scaling exponent or constant. When the collected data for non-anesthetized animals were fitted to this equation, the data showed an "anomalous" scaling for the minute ventilation against body mass (weight), with a scaling exponent close to but slightly higher than the theoretical value of 0.75.

The measured allometric scaling relationship for minute ventilation and body mass for the compiled data set is shown in Fig. 2. In particular, $\mathbf{V_m}$ displays a scaling range of about four decades with respect to **BW**, over which the observed relationship is seen to increase linearly on a double logarithmic plot. We conclude that $\mathbf{V_m}$ follows a power-law distribution of the form

$$(2) \qquad \mathrm{Log}_{10}\mathbf{V_m} = \boldsymbol{b} + \boldsymbol{a}\,\mathrm{Log}_{10}\mathbf{BW} \qquad \text{or} \qquad \mathbf{V_m} = \boldsymbol{k}\,\mathbf{BW}^{\mathbf{a}}$$

where $\boldsymbol{b} \equiv \mathrm{Log}_{10}\boldsymbol{k}$. A power-law distribution indicates the lack of a characteristic scale. A linear regression of the data collected gives values[2] for the constants in Equation 2 of: $\boldsymbol{b}$ = -0.286 ± 0.017 and $\boldsymbol{a}$ = 0.802 ± 0.011. This relationship explains 97.5% of the variation in the data. The least-squares fitted line is shown by the dotted line in Figure 2 and the solid lines delineate the 99% simultaneous confidence bands for the fitted line. In the form of Equation 2, the regression equation would be

$$(3) \qquad \mathrm{Log}_{10}\mathbf{V_m} = -0.286 + 0.802\,\mathrm{Log}_{10}\mathbf{BW} \qquad \text{or} \qquad \mathbf{V_m} = 0.518\,\mathbf{BW}^{0.802} \qquad r^2 = 0.975$$

where the units of minute volume $\mathbf{V_m}$ and of body weight **BW** are L/min and kg, respectively.

A normal quantile plot of the residuals from the least-squares fitted line (viz., the difference between the measured minute ventilation rates and the minute volumes predicted by Equation 3 : Fig. 3) shows that the residual distribution appears to be well approximated by a Gaussian distribution. Nevertheless, there does appear to be a small amount of skewness in the data at the extreme upper and lower tails of the residual distribution. Here, it is seen that the points in the upper and lower tails lie somewhat below and above the line, respectively, suggesting that the residual quantiles here are slightly smaller and larger, respectively, than what would have been expected for a Gaussian distribution. The influence of these points on the least-squares fit appears to be minimal. In particular, the use of a highly robust method for fitting a linear regression based on minimizing the sum of the $\boldsymbol{q}$ smallest squared residuals (*ie*, the least trimmed squares regression) gave essentially the same values for the parameters $\boldsymbol{a}$ and $\boldsymbol{b}$ [*cf.* Equation 2], namely[2] $\boldsymbol{b}$ = -0.286 ± 0.008 and $\boldsymbol{a}$ = 0.798 ± 0.007. Therefore, we consider the simple regression to be sufficient.

Interestingly, the observed allometric scaling relationship between $\mathbf{V_m}$ and **BW** yields a scaling exponent of 4/5 or 0.80, rather than the theoretical value of 3/4. The difference

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[2] Values are mean ± standard deviation

between these two values of scaling exponent is admittedly small, but this difference was statistically significant. Indeed, if a fitted function of the form of Equation 2 with $\boldsymbol{a}$ = 3/4 suffers from a lack of fit to the data, then the aspect of the underlying pattern not accounted for by the fit should be evident in the residuals. Figure 4 shows the residuals $\epsilon \equiv \mathrm{Log}_{10}\mathbf{V_m} - 0.75\ \mathrm{Log}_{10}\mathbf{BW}$ plotted against $\mathrm{Log}_{10}\mathbf{BW}$. Note that these residuals show a clear positive linear trend, implying that $\mathbf{V_m}$ varies with **BW** with a scaling exponent that is greater than the putative 3/4 provided by theory. The loess curve added shows the residual dependence of ϵ on $\mathrm{Log}_{10}\mathbf{BW}$. However, a plot of the residuals $\epsilon \equiv \mathrm{Log}_{10}\mathbf{V_m} - 0.80\ \mathrm{Log}_{10}\mathbf{BW}$ versus $\mathrm{Log}_{10}\mathbf{BW}$ (Fig. 5) does not appear to show any systematic trends. Indeed, fairing a loess curve through these residuals shows that the only variation appears to be a constant variation with $\mathrm{Log}_{10}\mathbf{BW}$; in particular, the constant value indicated by the loess curve for the residual variation is about -0.29 which coincides (approximately or better) with the least-squares fitted value for $\boldsymbol{b}$ = -0.286 ± 0.011.

A similar analysis was done with the data for anesthetized animals with a similar result. The resulting regression equations for the anesthetized animals were

$$(4)\qquad \mathrm{Log}_{10}\mathbf{V_m} = -0.509 + 0.782\ \mathrm{Log}_{10}\mathbf{BW} \qquad \text{or} \qquad \mathbf{V_m} = 0.310\ \mathbf{BW}^{0.786} \qquad r^2 = 0.927$$

where the units of minute volume $\mathbf{V_m}$ and of body weight **BW** are L/min and kg, respectively.

There were concerns that the contribution from small laboratory animals, which are physically and physiologically removed from man, would be over-emphasized because the numbers of studies and animals involved. If there was an such an effect, re-calculating the data using values weighted with the animal numbers should change the result in one direction and re-calculating the data using the mean values for each species should have an opposite effect. When these two extra calculations were performed, the resulting allometric equations were not significantly different and there was no apparent trend in the results. In fact, the effects noted on the non-anesthetized and anesthetized data sets appeared to be random. No further consideration was given to this topic.

The minute volume for a 70 kg man was calculated from Equation 3 (non-anesthetized animals) to be 15.6 L/min. From Equation 4 (anesthetized animals) the human minute volume was calculated to be 8.6 L/min. The 15.6 L/min value is within the bounds of accepted values for men doing "mild activity" [10, 11, 12, 13, 14] and slightly lower than the values measured in soldiers carrying light loads while walking on treadmills [15].

EVALUATION OF THE DATA PROVIDED BY PHALEN

There are three data sets quoted in a text by Phalen [7]. The first, taken from Crosfill and Widdicomb [1], is reproduced as part of Table I. The data are from anesthetized animals and generally show much lower breathing rates than the other studies. The second data table given in the book is adapted from a paper by Boyd and Mangos [70] which, in turn, was compiled from a number of papers describing of both non-anesthetized and anesthetized animals. The third table in Phalen's book is adapted from a paper by Mauderly [124] describing data from non-anesthetized animals. All of the original papers from these three studies have been obtained and the data is included in the data tables presented in this study. Comparison of the data in the three tables indicates the wide range of values for respiratory parameters that may be found in the literature. An allometric relationship was calculated for the Crosfill and Widdicomb [1] data to be

$$(5) \qquad \mathrm{Log}_{10}\mathrm{V}_{\mathbf{m}} = -0.485 + 0.810\ \mathrm{Log}_{10}\ \mathbf{BW} \qquad \text{or} \qquad \mathrm{V}_{\mathbf{m}} = 0.327\ \mathbf{BW}^{0.810} \qquad r^2 = 0.960$$

From this relationship, the human respiratory minute volume was calculated to be 10.2 L/min for a 70 kg man. As the data were appropriately included in the data tables of this review, no further work was done with these data sets.

RE-EVALUATION OF GUYTON'S DATA

The data used by Guyton [2; Table I] in his analysis were compiled and split into anesthetized and non-anesthetized groups and regression lines in the form of Equation 2 were calculated for each to be

Anesthetized

$$(6) \qquad \mathrm{Log}_{10}\mathrm{V}_{\mathbf{m}} = -0.386 + 0.750\ \mathrm{Log}_{10}\mathbf{BW} \qquad \text{or} \qquad \mathrm{V}_{\mathbf{m}} = 0.411\ \mathbf{BW}^{0.750}$$

Non-anesthetized

$$(7) \qquad \mathrm{Log}_{10}\mathrm{V}_{\mathbf{m}} = -0.458 + 0.763\ \mathrm{Log}_{10}\mathbf{BW} \qquad \text{or} \qquad \mathrm{V}_{\mathbf{m}} = 0.348\ \mathbf{BW}^{0.763}$$

and Guyton's published equation, when adjusted to the units used in this study[3], becomes

(8) $\text{Log}_{10}\mathbf{V_m} = -0.412 + 0.750\ \text{Log}_{10}\mathbf{BW}$ or $\mathbf{V_m} = 0.388\ \mathbf{BW}^{0.750}$

From these equations, it is obvious that the regression lines of the Log-Log format are very close to parallel (the slopes (***b***) are similar) and slightly separated (different intercept (***a***) values). The original, all combined Guyton data set produces a regression line that falls between those for the anesthetized and non-anesthetized animals. The slope of the equation for non-anesthetized animals is slightly steeper (0.763 vs 0.75).

For a 70 kg human the three Equations 6, 7 & 8, may be evaluated to give minute volume values of 9950, 8909 and 9372 cm^3/min or 10., 8.9 and 9.4 L/min for the minute volumes of men in similar physiologic states to the respective animal populations. These equations are very similar, differing slightly in slope and intercept with the result that the calculated human minute volumes are inverted - anesthetized less than non-anesthetized.

RE-EVALUATION OF SNIPES' DATA

The data quoted by Snipes [3] was treated in a similar manner to obtain the equations

(9) $\text{Log}_{10}\mathbf{V_m} = -0.273 + 0.741\ \text{Log}_{10}\mathbf{BW}$ or $\mathbf{V_m} = 0.533\ \mathbf{BW}^{0.741}$

where the minute volume $\mathbf{V_m}$ is in L/min and body weight **BW** is in kg.

A value of 12.4 L/min was obtained from these equations for a 70 kg man in similar physiologic condition. This value is not the value of 20 L/min given by Snipes adapted from Schlesinger [13] and Snyder *et al.*[14] for a 70 kg man doing "light activity".

3 The units used by Guyton were cm^3/min for the minute volume, V_m, and grams for the body weight, **BW**.

RE-EVALUATION OF THE EPA DATA SET

The United States Environmental Protection Agency (EPA) published recommended values [4] for animal growth, feeding, and respiration "... to be used only when the study under review does not report values for the biological variables required for the risk assessment... ". The data base has 87 papers yielding 203 entries encompassing 2570 animals of 44 species. Of these, 8 human studies contribute 22 entries and 301 "animals". Six papers are of wildlife of 17 species and in 17 of the 27 entries the numbers of animals are not reported. Nine species are birds and reptiles. In the remainder, the common laboratory species predominate. The data also include a number of studies with very young animals. Many of the studies are more recent than those reviewed here and, in the case of laboratory animals, more detailed as the different strains of the laboratory species are separately identified. Twenty-two of the 87 references are common to the current review and the EPA document. Unfortunately, those common references include both anesthetized and non-anesthetized animals and a number of the titles of the other references indicate that anesthetics may have been employed.

The EPA documents [4, 16] also give allometric equations for many of the species represented in their data base. However, the correlation coefficients are poor in comparison to that of the total data base and calculations of the minute volumes for the "standard" body weights produce some values that are considerably different from the experimental data. The use of the allometric equations for the separate species would appear to result in greater errors than would result from application of the total data base equations and, therefore, the presence of these "recommended" equations is noted and the use of same is discouraged.

The summary tables in the EPA document list the units of body weight as kg and of respiratory volume as m^3/day. The quoted equation for the relationship between daily respiration (minute volume) and body weight is

$$\text{(10)} \qquad \mathbf{I} = 0.66\ \mathbf{BW}^{0.7579}$$

where **I** is the daily respiration in m^3/day and **BW** is the body weight in kg. This equation becomes

$$\text{(11)} \qquad \mathrm{Log}_{10}\mathbf{V_m} = -0.339 + 0.758\ \mathrm{Log}_{10}\mathbf{BW} \quad \text{or} \quad \mathbf{V_m} = 0.458\ \mathbf{BW}^{0.758} \qquad r^2 = 0.96$$

when the units of minute volume ($\mathbf{V_m}$) are L/min and the body weights (**BW**) are in kg. We were unable to reproduce this regression from the published data base (data excluded by the EPA either included or excluded). Several attempts were made, without success, to reproduce the EPA equation with modified data including removing the human data, weighting the data by the animal numbers and working with the average values for each species. The following equations were calculated from the EPA data set

(12) $\mathrm{Log_{10}}\mathbf{V_m} = -0.384 + 0.763\ \mathrm{Log_{10}}\mathbf{BW}$ or $\mathbf{V_m} = 0.413\ \mathbf{BW}^{0.763}$ $r^2 = 0.960$

using minute volume ($\mathbf{V_m}$) in L/min, body weight (**BW**) in kg.

The minute volume values for a 70 kg human calculated from Equations 11 and 12 were 11.5 and 10.6 L/min, respectively.

DISCUSSION

The object of the exercise was to compile the data needed to obtain an estimate of the inhalation toxicity to soldiers (man) from inhalation toxicity values determined for a variety of animal species. To achieve this, a relationship must be established between the respiratory physiology of the animals and that of man. Three relationships that have been used and documented in the past are described and compared above [2, 3, 4]. The earliest and most quoted is that of Guyton [2] who used a mixture of anesthetized and non-anesthetized animals. When these are separated, the data becomes scant. Although, in the body weight/minute volume relationships (correlation regression lines) the slopes are only slightly different (0.750 vs 0.763), the intercept values are different and the predicted minute volumes for a 70 kg man differ by about 10%. In the data reported by Snipes [3], there are fewer species, no large species and the data could not be readily confirmed in published studies or reports. The minute volume for man calculated from the data was not the same as that quoted with the animal data. However, the data are quite similar to those generated for the present study. The third data set, from the EPA, also contains a mixture of non-anesthetized and anesthetized animals, a number of studies with very young animals and, upon close examination, relatively few studies albeit that they are generally more recent than those quoted by Guyton, Snipes and in this review. Comparisons of the regression equations (allometric equations) within the species with those between species in the EPA report clearly indicates that something is distorting the calculated results.

Although the allometric regression equation (Equation 8) of Guyton [2] could be reproduced, that of the EPA (Equation 6) could not. There are a number of plausible reasons for this. From the EPA reports [4, 16], it is neither clear what statistical approach nor what computational assistance (computer) were used to calculate their results and, further, nothing is said about mechanisms for use of incomplete data. There are many data in the EPA set that had missing animal numbers and there are birds and seals as well as reptiles (which were stated to have been disregarded). The discrepancies between our calculations and those reported by the EPA are a little large for round-off errors. Because the EPA reports do not give details concerning how the calculations were done in 1988, there is the possibility of computer concatenation of squared numbers in the statistical calculations if insufficient precision was used. Since we have not obtained all of the original documents referred to for the EPA study, there is also the possibility of typographical errors.

Theoretical considerations from allometric scaling models [9] indicate that the scaling exponent in the equations should be three-quarter power, in this case $\mathbf{BW}^{0.75}$. The data of Guyton [2], both anesthetized and non-anesthetized, fit very well to the predicted theoretical value of 0.75 or 3/4. The slope of the published equation in the EPA study (Equation 10) is close to 0.75. However, the same data when recalculated (Equations 12) gave a higher value. The slope values calculated in this study are slightly above 0.80 or 4/5 and the statistics clearly show a significant difference between the 0.75 and 0.80 values ($P < 0.01$). The 0.80 value has been obtained by others [5, 6, 17, 18, 19] and "...small deviations from quarter-power scaling sometimes occur [20, 21]." [9]. The data obtained clearly indicate that no artificial attempt should be made to force the body weight/minute volume relationship to fit the 3/4 power theoretical value.

The inter-species relationship between minute volume and body weight calculated from the data assembled for this review is considered by the authors to be the best currently available for use for military purposes. First and foremost, the calculated relationships fit, very closely, to the experimental data available. The data used are all from non-anesthetized mammals. Data from the very young have been removed. The majority of the data are from young adult animals and so match the target human population. Although there is a preponderance of data from laboratory species, the species range from very small to very large animals (mouse to giraffe) with a reasonable number in the sizes close to man. Finally, the number of studies, species and animals included in the calculations are large enough that the addition of more data should only result in small refinements rather than major alterations in the resulting body weight/minute volume relationship.

There remains a moot point; - would a calculation, weighted by animal numbers, provide an improved or better estimate of the relationship between body weight and minute volume? The statisticians will argue that the weighted values should be used. However, this adds importance, perhaps undue importance, to the data for small laboratory species because there are both more studies and more animals used per study. Biologically, therefore, the argument can be made to refrain from weighting the studies in an attempt to reduce the imbalance caused by large numbers of small laboratory animals. Indeed, in a recent US study [Reutter, S.A. & Wade, J.; personal communication], the average values for each species were used in an attempt to negate the imbalance in the numbers of large vs small animals. The current recommendation is to use the unweighted data from non-anesthetized animals and the corresponding theoretical human minute volumes to estimate human toxicities from animal toxicity data. Equations for anesthetized animals are presented so that they would be available for use with toxicologic studies in which anesthetics were employed.

The minute volume of resting healthy men apparently does not change with age in the adult [22]. Thus, for military purposes, there is no requirement to make corrections for age of the soldier. Since in general, men and women have similar minute volume to body weight ratios [14], there is no need to complicate matters with a separate set of respiratory values.

When toxicity, body weight and minute volume data are available, the data may be used directly to extrapolate the toxicity to a human estimate. However, in many cases the required respiratory and body weight measurements are not available for the subjects of toxicity studies and "standard" animal values must be applied. Examination of the data shown in Fig. 1 and Fig. 2 indicates that the minute volume and body weight vary in a similar manner both within and between species. The EPA study provides allometric equations for many of the species commonly used in toxicologic studies [4] albeit that the correlations reported for intra-species variation are not as good as that given for inter-species effects (probably because of the effect of very young animals on the relationships). From the mean and standard deviation values obtained in this study (Table IV), it is clear that the use of data for a "standard" animal will not create a large error if the test and "standard" animals are not too disparate. Indeed, the use of "standard" animal values allows "...assessments made by different individuals or groups at different times..." *to be* "... compared more clearly., allowing disagreements to focus on important scientific judgements rather than more mundane and trivial differences in assumptions of body weight and other biological variables." [4]. "Standard" animal values, given in Table III, were calculated using the recommended allometric relationship (Equation 3). The agreement with the collected data means is generally good. The mouse has the poorest agreement for the common laboratory species.

Since the physiologic state of all of the animals in a comparison should be as close as possible, the authors consider the best approach to be to use of the breathing rate for the required size of human that is calculated from the data presented in this treatise *eg.* 15.6 L/min for a 70 kg human. The appropriate values for a range of human body weights are given in Table II. In the other studies quoted, there is no general agreement on the minute volume value used for the human. Guyton [2] used a value, 6 L/min, for "resting" man which is lower than the 9.4 L/min value calculated from the data presented. Snipes [3], quoting Snyder [14], recommended a value of 20 L/min for man doing light activity but the data provided for the animals calculates to a value of 12.4 L/min for man. The EPA uses a combined value, also based upon Snyder, which provides a daily value for a man resting 8 hr and doing mild activity for 16 hr. The EPA equation provide human value of 10.6 L/min which also differs from the reference 20 L/min value. The ICRP Reference Man [14] breathes 23 m^3/day (15.9 L/min) during light activity (which is surprisingly close to the calculated value of 15.6 L/min from this study).

The allometric equations presented provide the relationship between body weight and minute volume for a fixed set of physiologic parameters. These equations cannot be used to calculate the toxicity for different breathing rates *eg.* for a 70 kg man breathing 30 L/min. The toxicity resulting from inhaling either an air dissolved chemical or an aerosol should be directly related to and vary with the volume of contaminated air inhaled which may be represented by the minute volume. Therefore, the calculation of toxicity values for breathing rates other than that indicated from the allometric relationship should be a simple inverse proportion (as the toxicity increases the LCt_{50} or LD_{50} decreases). For example, the LCt_{50} value for 70 kg human breathing 30 L/min would be 15.6/30 or 0.52 times the LCt_{50} value for a human breathing 15.6 L/min.

SUMMARY

The literature values for respiration of many species of animals have been gathered, collated and reviewed. The data base selected from the data collected, representing unanesthetized, young adult, mammals cover 18 species tabulating 134 experimental groups and data from 2304 animals. The animals range in size from mice at 12 g to horses and a giraffe at 480 - 550 kg.

The relationship between body weight and respiratory minute volume was re-investigated using a larger, more directed data base than those used in previous studies. An allometric regression equation relating body weight and minute volume was obtained;

$$\mathrm{Log}_{10}\mathbf{V}_{\mathbf{m}} = -0.286 + 0.802\ \mathrm{Log}_{10}\mathbf{BW} \quad \text{or} \quad \mathbf{V}_{\mathbf{m}} = 0.518\ \mathbf{BW}^{0.802} \quad r^2 = 0.975$$

The corresponding value, obtained from this allometric equations, for a 70 kg human under similar physiologic conditions was estimated to be 15.6 L/min. A table of minute volumes for various human body weights is provided.

In the judgement of the authors, the allometric relationship and the data presented represent the best currently available for use in the estimation of human inhalation toxicity for awake and lightly active soldiers.

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Table IV

Average Body weights, minute volumes and MV/BWt for non-anesthetized animals

Species	Body Weight (kg)	Minute Volume (L)	Minute Volume / B Wt	Species	Body Weight (kg)	Minute Volume (L)	Minute Volume / B Wt
Cat	3.36^{32,5} ±0.480	0.845 ±0.061	0.257 ±0.052	Pony	167^{3,3} ±35	29.4 ±13.8	0.183 ±0.092
Cows	370^{68,19} ±147	71 ±33	0.189 ±0.047	Horse	465^{27,4} ±29	62 ±14	0.133 ±0.029
Donkey	120.^{1,1}	19.5	0.16	Mule	210^{2,2}	25.9	0.12
Dog	13.0^{739,21} ±11.5	4.41 ±1.99	0.368 ±0.089	Sheep	52.6^{46,11} ±15.2	13.9 ±7.2	0.289 ±0.160
G pig	0.317^{483,13} ±0.129	0.179 ±0.039	0.616 ±0.161	Pig	197^{2,2} ±39	28 ±13	0.138 ±0.037
Goat	36.9^{38,4} ±12.3	9.6 ±2.8	0.263 ±0.052	Giraffe	544.^{2,1}	74	0.136
Hamsters	0.111^{97,4} ±0.016	0.051 ±0.008	0.474 ±0.142	Rabbit	2.77^{61,3} ±0.63	1.453 ±0.193	0.413 ±0.787
Mouse	0.021^{74,4} ±0.007	0.031 ±0.014	1.491 ±0.366	Rat	0.259^{314,21} ±0.073	0.211 ±0.078	0.881 ±0.437
*Cotton rat	0.077^{27,1}	0.040	0.516	Baboon	4.42^{4,1}	1.61	0.365
*Spiny anteater	3.47^{3,1} ±0.177	0.527 ±0.251	0.150 0.065	Monkey	4.27^{311,15} ±2.69	1.40 ±0.42	0.374 ±0.125

Superscript values on the body weight data are (number of animals, number of studies)

* Excluded from analysis, See text.

Table V

Average Body weight, minute volume and MV/BWt for anesthetized animals

Species	Body Weight (kg)	Minute Volume (L)	Minute Volume / B Wt
Cat	3.06[94,12] ±0.393	0.707 ±0.271	0.226 ±0.066
Dog	11.6[135,11] ±4.0	2.64 ±1.44	0.234 ±0.112
Ferret	0.314[18,1]	0.195	0.621
G pig	0.583[53,2] ±0.151	0.142 ±0.017	0.256 ±0.095
Hamsters	0.121[114,6] ±0.015	0.043 ±0.016	0.372 ±0.170
Mouse	0.025[46,6] ±0.005	0.026 ±0.016	1.044 ±0.588
Sheep	41.8[25,3] -[a]	8.51 ±3.7	0.204 ±0.083
Pig	28.[19,1]	6.7	0.24
Giraffe	544.[1,1]	61.	0.111
Rabbit	2.89[74,5] ±1.12	0.67 ±0.14	0.251 ±0.085
Rat	0.289[397,22] ±0.173	0.129 ±0.046	0.524 ±0.184
Monkey,	3.75[127,23] ±1.09	0.891 ±0.397	0.235 ±0.065

Superscripts in the body weight column are (number of animals, number of experiments) involved in the mean values.

[a] Body weight value for sheep is artificial, calculated from a minute volume provided as $L/min/m^2$ body surface using the formula given by the author for calculating surface area from body weight. The value for minute volume is the quoted value in $L/min/m^2$ and the body weight value is the corresponding weight in kg for one m^2.

Table VI

Comparisons of respiratory function and body weight
Summary of data collected; non-anesthetized animals

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / Body Wt	Reference
Monkey	chair, 30 min	2.80	60	1.487	0.531	63
Monkey	str. jacket, 30 min	2.80	60	1.587	0.567	63
Monkey	sedated, conscious	3.00	3	1.000	0.333	82
Monkey	sedated	3.50	16	1.200	0.343	83
Monkey	sedated	3.50	3	1.400	0.400	83
Monkey		2.68	6	0.863	0.322	93
Monkey, Rhesus	chair	10.70	3	2.000	0.187	103
Monkey, Rhesus	chair	10.90	6	2.000	0.183	103
Monkey, Rhesus	untrained, quieted	2.63	39	1.014	0.386	109
Monkey, Rhesus	untrained, quieted	3.49	4	0.757	0.217	109
Monkey, Rhesus	conscious, O_2	4.05	4	1.100	0.272	119
Monkey, female, Rhesus	chair	3.33	8	1.820	0.547	66
Monkey, male, Rhesus	chair	3.48	8	1.441	0.414	66
Monkey, cynom	chair	4.25	10	2.039	0.480	65, 66
Monkey, cynom	chair	3.00	81	1.272	0.424	51
*Monkey, pygmy	Free, infant	0.68	1	0.400	0.588	106
Baboon	chair	4.42	4	1.612	0.365	65, 66
Cat	trained, free	3.00	4	0.804	0.268	60
Cat	trained, awake, not purring	3.40	6	0.840	0.247	88
Cat	trained, plethysmograph	2.80	11	0.950	0.339	87
Cat	trained	3.62	6	0.830	0.229	89
Cat	trained, plethysmograph	4.0	5	0.8	0.2	90
**Cat	trained, plethysmograph	2.23	4	0.475	0.213	152
**Cat	trained, plethysmograph	2.55	4	0.490	0.192	152
**Cat	trained, plethysmograph	2.58	4	0.373	0.145	152
**Cat	trained, plethysmograph	2.35	4	0.284	0.121	152
Cows,	standing, stanchion	439.	4	78.4	0.179	141
*Calves, Ayrshire 8 mo	Standing, stanchion	147.	4	31.3	0.213	94
Cows, Br.Swiss,	stanchion, raised 50F	250.	3	44.0	0.176	112, 156
Cows, Br.Swiss,	stanchion, raised 50F	325.	3	50.2	0.154	112, 156
Cows, Brahmin	stanchion, raised 80F	350.	3	37.9	0.108	112, 156
Cows, Brahmin,	stanchion, raised 80F	250.	3	34.0	0.136	112, 156
Cows, Guernsey	stanchion	435.	2	126.7	0.291	56
Cows, Guernsey,	Standing	410.	1	107.0	0.261	53, 95

* Excluded as too young

** Excluded as outlier, See text.

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Table VI Continued; non-anesthetized animals

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / B Wt	Reference
Cows, Hereford,	Standing	422.	1	109.0	0.258	53, 95
Cows, Hereford,	Standing	144.	1	49.0	0.340	53, 95
Cows, Holstein,	Standing	514.	1	114.0	0.222	53, 95
Cows, Holstein,	Standing	164.	1	61.0	0.372	53, 95
Cows, Holstein,	stanchion, raised 50F	250.	3	51.4	0.206	113
Cows, Holstein,	stanchion, raised 50F	350.	3	66.5	0.190	113
Cows, Jersey	stanchion	340	1	59.3	0.174	56
Cows, Jersey,	Standing	403.	1	92.0	0.228	53, 95
Cows, Jersey,	stanchion, raised 50F	225.	3	39.1	0.174	113
Cows, S.Gertrudis	stanchion, raised 80F	250.	3	49.7	0.199	113
Cows, S.Gertrudis	stanchion , raised 80F	350.	3	55.9	0.160	113
Cows, Shorthorn	stanchion raised 50F	250.	3	45.8	0.183	113
Cows, Shorthorn	stanchion raised 50F	350.	3	49.1	0.140	113
*Cows, Guernsey	stanchion, raised 50°F	110	3	5.6	0.051	112, 156
*Cows, Br.Swiss,	stanchion, raised 50F	100.	3	23.7	0.237	112, 156
*Cows, Brahmin,	stanchion, raised 80F	100.	3	19.1	0.191	112, 156
*Cows, Hereford, 4-6 wk	plethysmograph	59.	8	13.1	0.222	67
*Cows, Holstein,	stanchion, raised 50F	100.	3	25.5	0.255	113
*Cows, Jersey,	stanchion, raised 50F	100.	3	21.9	0.219	113
*Cows, S.Gertrudis	stanchion, raised 80F	100.	3	27.4	0.274	113
*Cows, Shorthorn	stanchion, raised 50F	100.	3	35.4	0.354	113
Dog, Beagle		11.3		3.60	0.319	125
Dog, Beagle		11.2		3.90	0.348	125
Dog, Beagle 13 months,	5500 ft, Albuquerque NM	9.2	39	5.28	0.577	142
Dog, Beagle		10.5	20	3.14	0.299	155
Dog, Beagle	1 year	9.2	140	3.60	0.391	125
Dog, Beagle	5 year	11.2	48	3.90	0.348	125
Dog, Beagle	10 year	11.3	50	3.60	0.319	125
Dog, Beagle	restrained	9.6	49	4.47	0.465	122
Dog, Beagle, female	12-14 mo	8.4	50	3.60	0.429	123
Dog, beagle, female	3-4 yr	10.0	10	3.61	0.361	123
Dog, Beagle, female	8-10.5 yr	10.9	36	3.81	0.350	123
Dog, beagle, male	12-14 mo	10.0	50	3.65	0.365	123
Dog, beagle, male	3-4 yr	12.0	10	4.51	0.376	123
Dog, Beagle	trained, free	9.0	12	3.30	0.367	129
Dogs		9.0		3.70	0.411	118, 124
Dog	restrained plethysmograph	59	1	11.7	0.1981	56
Dog	restrained plethysmograph	13.5	1	6.6	0.489	56

* Excluded as too young
** Excluded as outlier, See text.

Table VI Continued; non-anesthetized animals

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / B Wt	Reference
Dog	restrained plethysmograph	15.6	5	3.41	0.219	99
*Dog, Beagle	0.25 year	3.1	10	1.80	0.581	125
G pig	free	0.466	61	0.156	0.334	93
G pig	trained, free	0.512	10	0.171	0.334	129
G pig	trained, free	0.194	8	0.162	0.835	133
G pig	trained, free	0.212	5	0.154	0.724	133
G pig	restrained	0.345	24	0.236	0.684	92
G pig	restrained	0.245	26	0.157	0.641	52
G pig	plethysmog, intrathoracic catheter	0.219	200	0.139	0.635	54
G pig	plethysmog, intrathoracic catheter	0.215	85	0.139	0.644	54
G pig	plethysmog, intrathoracic catheter	0.209	60	0.137	0.656	54
G pig	free	0.588	1	0.226	0.384	85
G pig	free	0.312	1	0.209	0.670	85
G pig	free	0.278	1	0.204	0.733	85
G pig	free	0.329	1	0.242	0.736	85
Goat	trained, masked	52.5	3	12.3	0.235	153
Goat	laterally recumbent, awake	23.7	21	5.7	0.242	58
Goat	stanchion	31.5	4	10.7	0.341	56
Goat	trained, masked	40.0	10	9.4	0.235	140
Hamster	free	0.111	10	0.050	0.452	128
Hamster	trained, free	0.110	10	0.050	0.455	129
Hamster	quiet, (asleep?)	0.130	12	0.042	0.323	74
Hamster	free	0.092	65	0.061	0.665	93
Mouse	free	0.0198	56	0.0245	1.239	93
Mouse		0.0271	5	0.0520	1.919	151
Mouse		0.0120	6	0.0200	1.667	120
*Mouse,	free	0.0105	10	0.0150	1.429	114
Mouse, C57	free	0.0240	7	0.0273	1.138	86
Pony	free	205.	1	19.9	0.097	124
Pony	free	135.	1	23.2	0.172	124
Pony	free	161.	1	45.2	0.281	124

* Excluded as too young
** Excluded as outlier, See text.

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Table VI Continued; non-anesthetized animals

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / B Wt	Reference
Horse, Morgan	Treadmill trained	476.	5	65.	0.137	150
Horse	standing	422.	2	60.	0.142	131
Horse, Thoroughbred	standing	486.	15	79.	0.163	91
Horse, mixed	standing tied	476.	5	44.	0.093	56
Donkey	stanchion	120.	1	19.5	0.163	56
Mule	stanchion	210	1	30.1	0.143	56
Mule	stanchion	210	1	21.7	0.103	56
Rabbit	trained free	3.00	9	1.240	0.413	129
Rabbit	Awake, restrained	3.25	10	1.503	0.463	143
Rabbit	trained, free	2.05	42	1.615	0.787	118, 59
Rat	free	0.400	16	0.223	0.558	118, 60
Rat	trained, free	0.383	10	0.215	0.561	129
Rat, white	free	0.310	1	0.066	0.213	131
Rat	head electrodes	0.300	5	0.141	0.470	139
Rat	Quiet, awake	0.300	5	0.153	0.510	138
Rat,	Porton	0.198	5	0.199	1.008	121
Rat, 18 week	free	0.299	10	0.225	0.753	117
Rat, 10 week	free	0.211	10	0.161	0.761	117
Rat, 3-6 mo	plethysmog, whole body	0.303	36	0.273	0.899	134
Rat, 3-6 mo	plethysmog, whole body	0.303	67	0.236	0.780	134
Rat	trained, free	0.250	16	0.140	0.560	60
Rat	trained, free	0.250	12	0.155	0.625	60
Rat		0.284	8	0.276	0.971	115
Rat	unrestrained	0.305	8	0.214	0.701	115
Rat		0.250	4	0.238	0.950	135
Rat	free	0.198	5	0.199	1.008	121
Rat	free	0.238	14	0.388	1.630	135, 73
Rat	free	0.229	14	0.336	1.467	135, 69
Rat	free	0.111	23	0.228	2.054	135, 69
*Rat, white	free	0.113	35	0.073	0.646	93
*Rat, 5 week	free	0.052	10	0.087	1.662	117
*Rat, 7 week	free	0.110	10	0.113	1.028	117
**Cotton rat	free	0.077	27	0.040	0.516	93

* Excluded as too young
** Excluded as outlier, See text.

Table VI Continued; non-anesthetized animals

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / B Wt	Reference
Sheep	stanchion	52.0	1	28.0	0.539	56
Sheep	Thermoneutral water bath	59.9	4	7.10	0.119	53, 100
Sheep	Air	77	1	10.2	0.133	101
Sheep	Air	71	1	9.4	0.133	101
Sheep	Thermoneutral water bath	70	1	11.4	0.163	101
Sheep	20°C environment	52.0	1	28.0	0.538	56
Sheep	Temperature study	29.0	2	13.8	0.477	68
Sheep[a]	light thiopentone	41.8	13	12.53	0.300	77
Sheep[a]	light thiopentone	41.8	9	11.34	0.271	77
Sheep[a]	light thiopentone	41.8	2	9.91	0.237	77
Sheep[a]	light thiopentone	41.8	11	11.39	0.272	77
Pig, female, 6 mo	Restrained	170	1	19	0.112	56
Pig, female		225		37	0.164	53, 71
Giraffe	Free standing	544	2	74.3	0.136	141
**Spiny Anteater	♀, Quiet, restrained, asleep?	3.35	2	0.350	0.136	62
**Spiny Anteater	♂, Quiet, restrained, asleep?	3.60	1	0.704	0.196	62
Marine mammals[b]						
Harbour seal	Cheyne-Stokes respiration	27.5		3.97	0.144	104
Porpoise	In captivity	170		9.7	0.057	105
Killer whale	Beached, free	1090	1	47.8	0.044	147

* Excluded as too young

** Excluded as outlier, See text.

[a] Body weight value sheep is a minute volume provided as L/min/m^2 body surface and the body weight value is the corresponding weight in kg for one m^2.

[b] Excluded for physiologic reasons, See text.

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Table VII

Comparisons of respiratory function and body weight
Summary of data collected; anesthetized animals

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / B Wt	Reference
Cat	pentobarbital Na	3.70	4	0.960	0.259	1
Cat	pentobarbital Na	3.25	6	0.785	0.242	146
Cat	pentobarbital Na	2.80	6	0.410	0.146	130
Cat	pentobarbital Na	2.80	11	0.550	0.196	87
Cat	pentobarbital Na	3.20	9	1.076	0.336	154
Cat	pentobarbital Na	3.40	6	0.840	0.247	88
Cat	pentobarbital Na	3.40	6	0.900	0.265	88
Cat	pentobarbital Na	2.7	5	0.5	0.19	90
Cat	pentobarbital Na	2.5	6	0.468	0.187	156
Cat	ketamine	3.10	10	0.489	0.158	107
Cat	diazepam	3.40	6	1.130	0.332	88
Cat	nembutal	2.55	4	0.250	0.098	152
Cat	chloralose	2.60	4	0.180	0.069	152
Cat	urethane	2.35	4	0.248	0.105	152
Cat	alpha chloralose	2.50	19	0.381	0.152	61
Dog	nembutal	13.5	39	6.22	0.462	57
Dog	nembutal	10.0	8	4.00	0.400	149
Dog	pentobarbital	12.6	4	3.10	0.246	1
Dog, no breed	chloralose/ethyl carbamate	9.3	2	1.07	0.115	132
Dog, no breed, females	pentobarbitol	16.8	35	1.81	0.108	97
Dog, no breed, males	pentobarbitol	21.0	42	2.92	0.139	97
Dog, Beagle, 560-700 days	pentobarbital+vetame	9.0	1	1.68	0.186	78
Dog, Beagle, 560-700 days	pentobarbital+vetame	9.0	1	1.76	0.195	78
Dog, Beagle, 560-700 days	pentobarbital+vetame	9.0	1	1.82	0.202	78
Dog, Beagle, 560-700 days	pentobarbital+vetame	9.0	1	2.16	0.239	78
Dog, Beagle, 560-700 days	pentobarbital+vetame	9.0	1	2.48	0.276	78
Pig	nembutal	28.	19	6.7	0.239	57
Sheep	NA thiopentone	41.8[a]	5	6.35	0.152	96
Sheep	Na thiopentone	41.8[a]	7	6.67	0.159	76
Sheep	Na thiopentone	41.8[a]	13	12.53	0.300	76
Ferret	pentobarbital	0.314	18	0.195	0.621	70

[a] Body weight value for sheep is artificial calculated from a minute volume provided as L/min/m^2 body surface using the formula given by the author for calculating surface area from body weight. The value for minute volume is the quoted value in L/min/m^2 and the body weight is the corresponding weight in kg for one m^2.

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Table VII Continued

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / B Wt	Reference
G pig	pentobarbital Na	0.690	4	0.130	0.188	1
G pig	ether	0.477	49	0.154	0.323	93
Hamster, male	pentobarbital Na	0.132	27	0.045	0.341	144
Hamster, female	pentobarbital Na	0.136	27	0.040	0.294	144
Hamster	ether	0.096	34	0.048	0.499	144
Hamster	chloralose/ethyl carbamate	0.110	7	0.072	0.650	132
Hamster, 15 week	halothane	0.126	10	0.028	0.221	126
Hamster, 65 week	halothane	0.125	9	0.028	0.225	126
Giraffe	Free standing	544	1	61	0.111	141
Mouse	pentobarbital Na	0.0320	4	0.0210	0.656	1
Mouse	pentobarbital	0.0271	5	0.0207	0.764	151
Mouse	chloralose/ethyl carbamate	0.0270	10	0.0560	2.074	132
Mouse	ether	0.0188	7	0.0177	0.941	93
Mouse	ether	0.0207	15	0.0281	1.357	93
Mouse, C57	pentobarbital Na	0.0230	5	0.0108	0.470	86
Rabbit	pentobarbital Na	2.400	4	0.620	0.258	1
Rabbit	chloralose/ethyl carbamate	1.800	4	0.450	0.250	132
Rabbit	ether	2.069	31	0.800	0.387	93
Rabbit, 0.5-1 yr	pentobarbital Na	4.100	15	0.773	0.188	80
Rabbit, 3-5 yr	pentobarbital Na	4.100	20	0.694	0.169	80
Rat	chloralose/ethyl carbamate	0.215	16	0.152	0.707	132
Rat	urethane	0.163	21	0.119	0.732	135
Rat	urethane	0.230	18	0.146	0.635	135
Rat	urethane	0.285	24	0.171	0.600	135
Rat	urethane	0.323	14	0.127	0.393	75, 137
Rat	urethane+allobarbital	0.195	10	0.092	0.472	135, 75, 137
Rat	halothane	0.200	20	0.054	0.270	79
Rat	urethane	0.206	67	0.085	0.416	135, 136
Rat	urethane	0.210	10	0.288	1.371	135
Rat	halothane, light	0.229	10	0.203	0.886	135
Rat	halothane, light	0.220	10	0.132	0.600	135
Rat	halothane, light	0.234	9	0.149	0.637	135
Rat	halothane, light	0.266	8	0.189	0.711	135
Rat	halothane, light	0.280	7	0.115	0.411	135
Rat	pentobarbital Na	0.250	4	0.160	0.640	1

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Table VII Continued

Species	Physiological state and details	Body Weight (kg)	Number of animals	Minute volume (Litres)	Minute volume / B Wt	Reference
Rat, female, B&W Hooded	pentobarbital Na	0.257	28	0.111	0.432	144
Rat, male, B&W hooded	pentobarbital Na	0.464	30	0.207	0.446	144
Rat, Fisher, female	urethane	0.233	32	0.161	0.691	81
Rat, white	ether	0.110	32	0.076	0.688	93
Rat, white	thiamyl	0.402	12	0.175	0.435	108
Rat, 102 days	halothane	0.222	20	0.054	0.243	127
Rat, 538 days	halothane	0.334	10	0.082	0.246	127
Rat, 815 days	halothane	0.332	10	0.082	0.247	127
Monkey	sernyl	2.80	2	0.530	0.189	63
Monkey	pentobarbital Na	2.45	4	0.700	0.286	1
Monkey	ketamine	2.61	1	0.480	0.184	84
Monkey	ketamine	3.03	1	0.600	0.198	84
Monkey	ketamine	3.53	1	0.900	0.255	84
Monkey	ketamine	3.33	1	0.900	0.270	84
Monkey	ketamine	3.32	1	0.800	0.241	84
Monkey	ketamine	2.71	1	0.750	0.277	84
Monkey	ketamine	3.66	1	1.100	0.301	84
Monkey	ketamine	3.31	1	1.000	0.302	84
Monkey	ketamine	3.50	1	0.900	0.257	83
Monkey	ketamine	3.50	1	1.000	0.286	83
Monkey	pentobarbital	3.50	1	0.546	0.156	114
Monkey, Rhesus	pentobarbital	7.56	6	1.71	0.226	98,148
Monkey, Rhesus	tileamine	3.30	10	0.462	0.140	64
Monkey, Rhesus	ketamine+acepromazine	3.30	10	0.442	0.134	64
Monkey, Rhesus	ketamine	3.30	10	0.575	0.174	64
Monkey, Rhesus	pentobarbital	4.25	11	1.650	0.388	72, 148
Monkey, Rhesus	pentobarbital	7.60	8	3.860	0.508	148
Monkey, Rhesus	pentobarbital	3.49	4	0.681	0.195	109
Monkey, Rhesus	pentobarbital	4.30	21	0.709	0.165	111
Monkey, Rhesus	phencyclidene	5.80	14	1.791	0.309	116, 148
Monkey, Rhesus	pentobarbital, O_2	5.05	9	0.900	0.178	119
Monkey, Rhesus	pentobarbital	5.05	9	1.360	0.269	119

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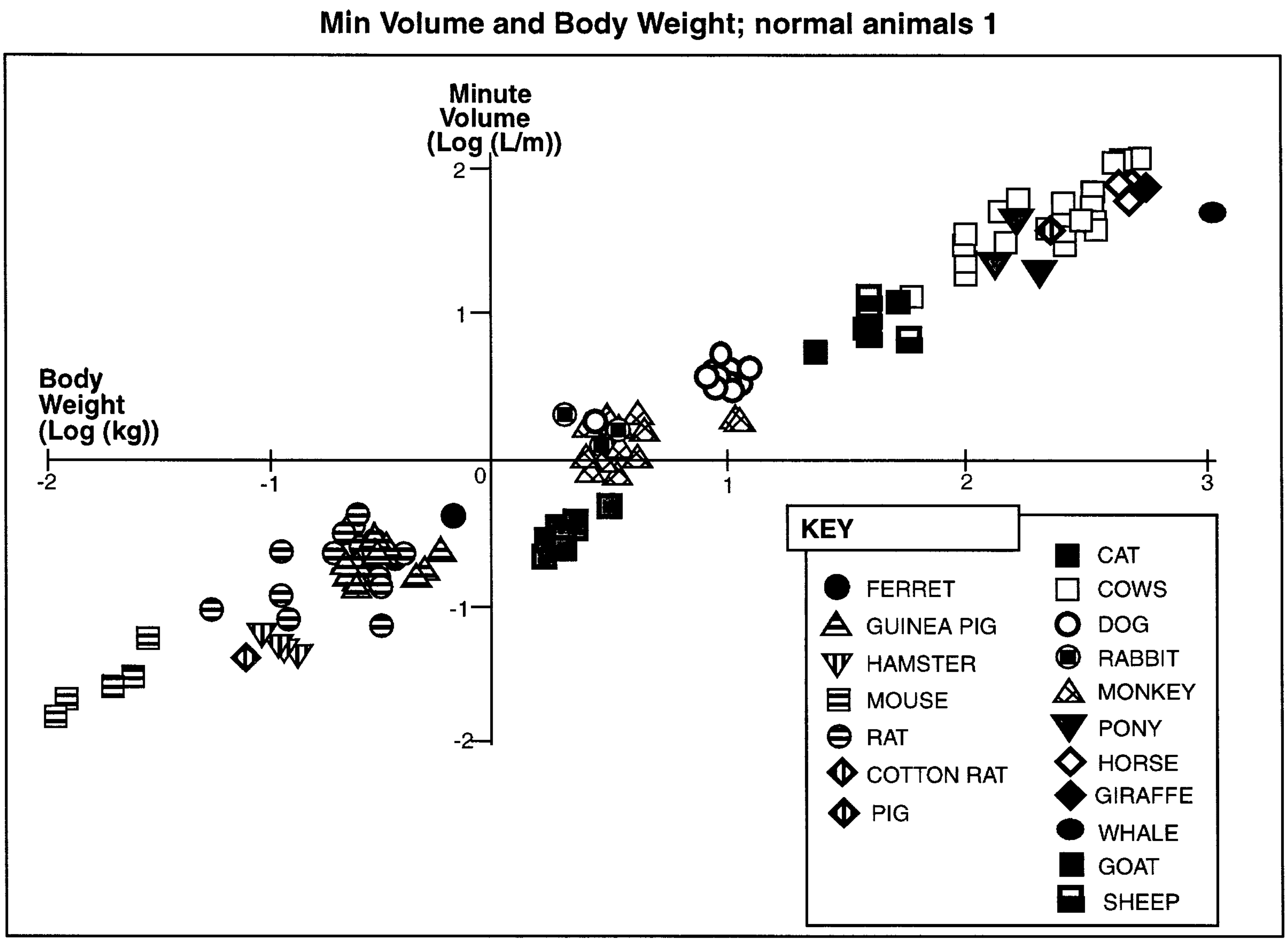

Fig. 1 Body weight and minute volume of representative animal data in the collected data base. The data show an allometric relationship on this Log-Log plot that is linear and flows readily through the data. The data represent a range from a mouse (12 g) to a whale (1090 kg).

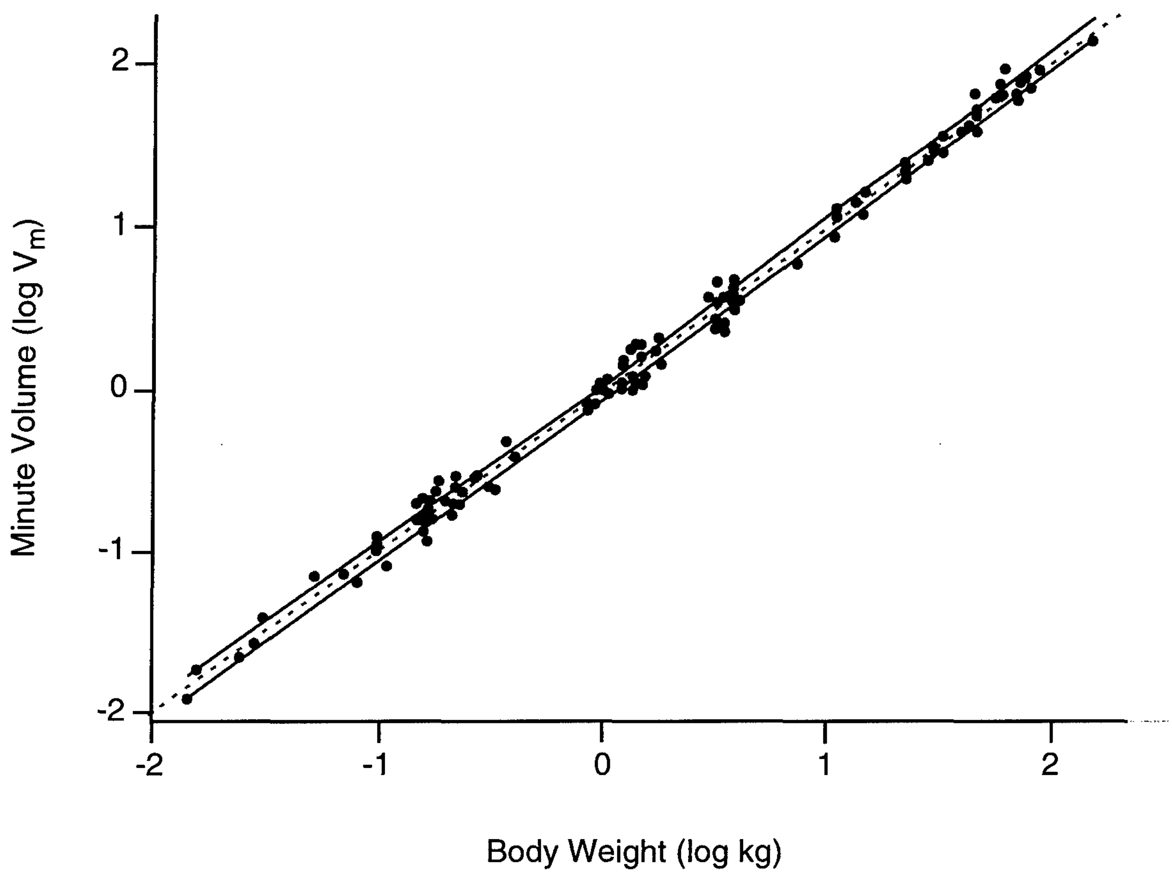

Fig. 2 A statistical plot of the allometric equation for non-anesthetized animals and the statistical error limits. For this plot, the final data set was used. Marine mammals, very young animals and several groups of outlying data have been excluded. The fit of the regression line is very good; $r^2 = 0.975$.

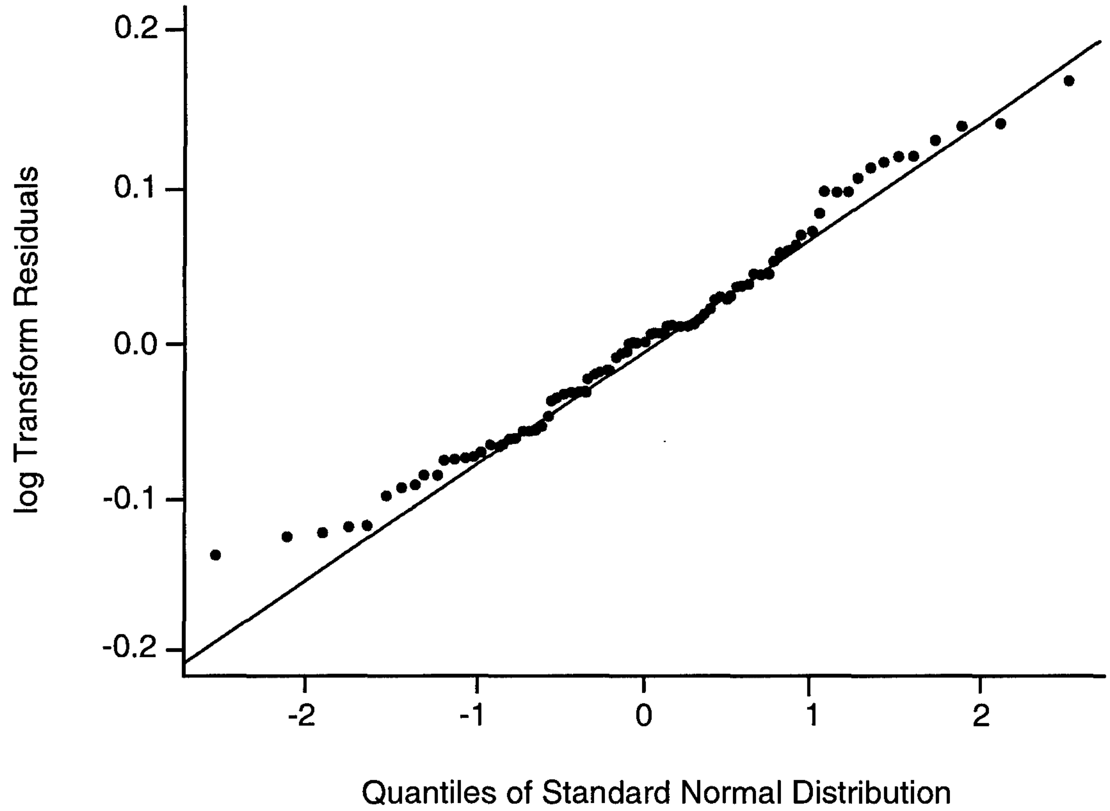

Fig. 3 A quantile plot of the residuals from the fitted line describing the difference between the measured and the predicted logarithmic minute ventilation rates.

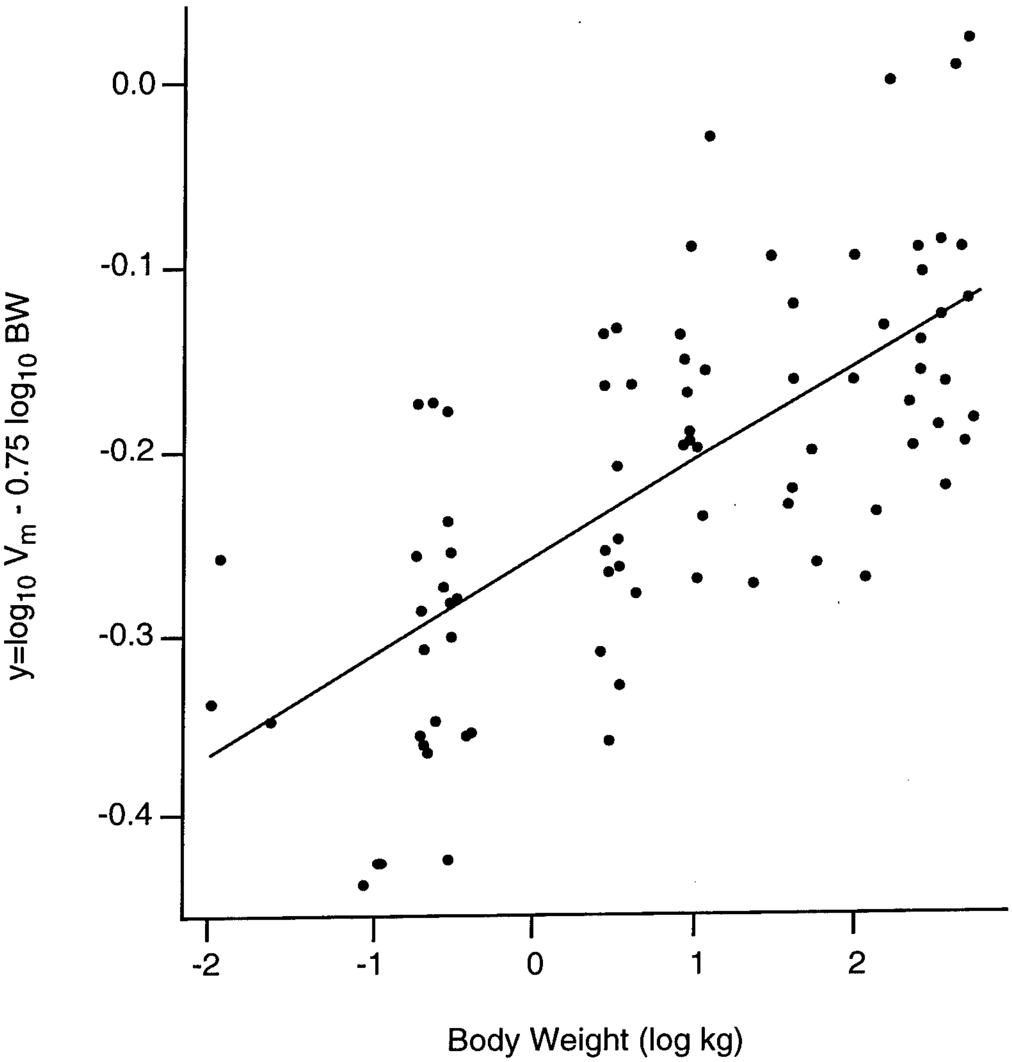

Fig. 4 When the power-law exponent is assumed to be 3/4, the plot of residuals vs body weight indicates an upward trend. This suggests that V_m varies with **BW** with a greater than 3/4 scaling component.

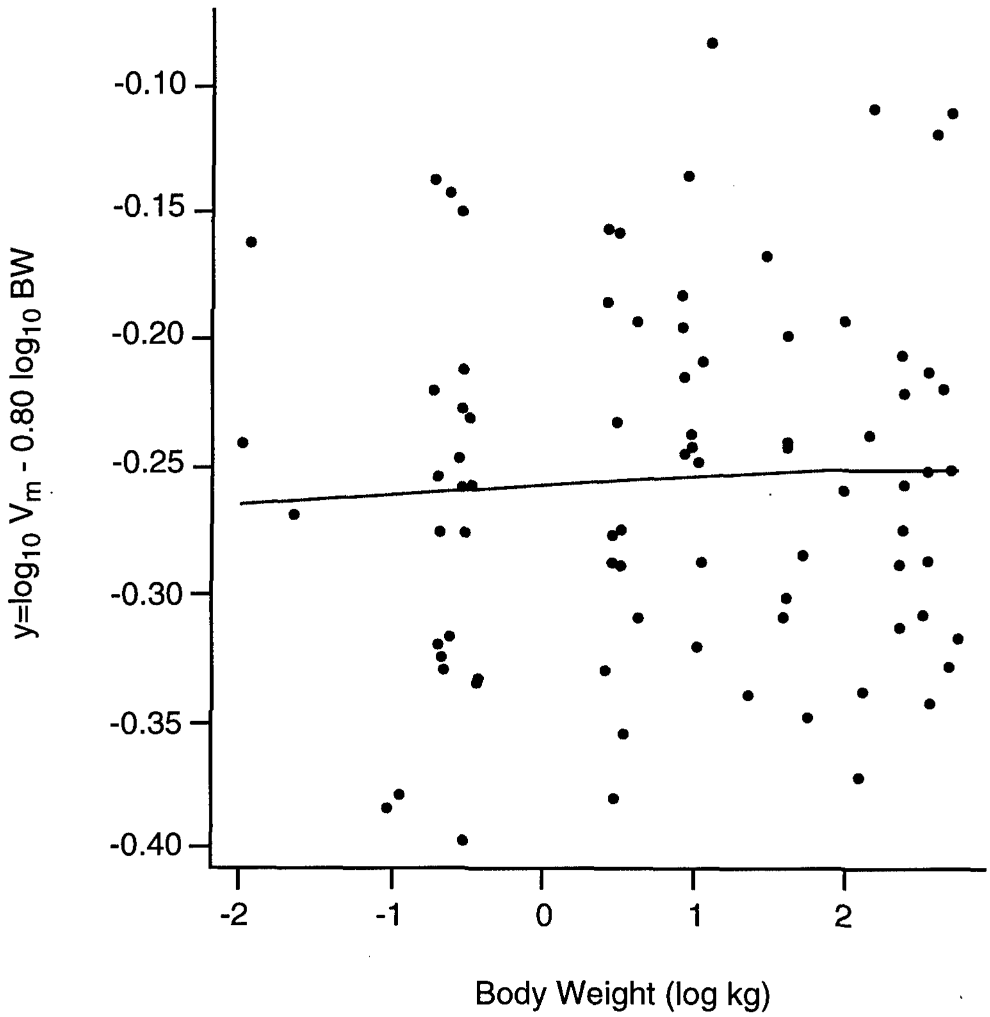

Fig. 5 When the power-law exponent is 0.80, the plot of residuals vs body weight does not show any systematic trends suggesting that all of the variability in the data is accounted for in the allometric equation.

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1. Minute Volume - Body Weight Relationships Between Animals and Man

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Bide, R.W.; Armour, S.J. and Yee, E.

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The relationship between body weight (BW) and respiratory minute volume (V_m) was reviewed by collecting a data base from the literature of minute volume rates that encompassed species from mice at 12 g body weight to horses and a giraffe at ≈500 kg body weight. The data were separated into anesthetized and non-anesthetized groups and juvenile animals were removed from the non-anesthetized group. The final data set of non-anesthetized animals contained 131 studies representing 2125 animals and 18 species. The data show a power-law (allometric) relationship between the minute volume and body weight. The scaling or allometric parameters in this power-law have been estimated using a linear regression of the logarithms of the minute volume against body weight. The resulting allometric equations were;

$$\mathrm{Log}_{10}V_m = -0.286 + 0.802\ \mathrm{Log}_{10}BW \qquad \text{or} \qquad V_m = 0.518\ BW^{0.802}$$

From these equations a corresponding set of minute volumes were obtained for various body weights of humans *eg.* 15.6 L/min for a 70 kg human. The results of the analyses were compared to similar studies in the literature. The relationship is recommended for military uses because it is derived from non-anesthetized, young adult mammals which are expected to mimic the soldier.

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